REMARKS

Prior to entry of the present amendment, claims 34-65 are pending. Claims 46 and 48-57, due to a Restriction Requirement, are withdrawn from consideration. Claims 34-40, 42-45, 47, and 58-64 are rejected under 35 U.S.C. § 112, first paragraph. Claims 41 and 65 are objected to. Applicants address each basis for rejection as follows.

Amendments to the claims

Claims 34-45 and 61-63 have been cancelled.

A minor typographical error has been corrected in withdrawn claim 49.

Claim 58 has been re-written in independent form and now recites an inhibitory antibody against Factor VIII, and recites mutations at positions Asn47 and/or Thr49 instead of at positions 47 to 49, or the deglycosylation of Asn 47. Support for the amendment to recite deglycosylation of Asn 47 is found, for example, in the application at page 6, lines 8-11, at page 12, lines 5-14, at page 26, line 22, to page 27, line 9, and Figure 17 of the WO 2005/016455 publication. Here the specification states:

> The modification of glycosylation is optionally obtained by exposing the native antibodies or fragments thereof to carbohydrate cleaving or transforming enzymes. (page 6, lines 8-11)

and

> [T]he pharmaceutical compound comprises one or more monoclonal antibodies which have been modified in the glycosylation in the region Asn47-Thr49 ... Alternatively, this modification is obtained by contacting the native Krix-1 antibody or fragments thereof with conditions which ensure modification of the glycosylation at Asn47-49 (such as increased levels of deglycosylation enzymes[)]. (page 12, lines 5-14)

and

> Removal of the glycosylation of Krix-1 at Asn47 in the consensus glycosylation sequence Asn47-X-Thr49-Y can be achieved in several ways. (page 26, lines 22-23)

Recitation of the phrase "at least 90 % sequence similarity" has been deleted from claim 58.

Claim 64 has been re-written in independent form and now recites an inhibitory antibody against Factor VIII, and recites mutations at position 3 and/or 5 of CDR1 instead of at positions 3 to 5, or the deglycosylation of Asn at position 3 of CDR1 (language analogous to that recited in claim 58). Claim 64 as amended refers to the CDRs as "regions" instead of "sequences."

New claim 66 has been added. Claim 66 defines the inhibitory antibody by the 3 CDR regions of the immunoglobulin variable heavy chain, and more specifically is directed to the subject matter of former claim 42 which recited the variable heavy chain with the sequence of SEQ ID NO:2. The designation of the mutated residues and the glycosylation site in claim 66 as amended is that described above for claim 64.

New claims 67, 68, and 69 have been added, and these claims recite the scFv fragment recited in former claim 41 (now cancelled).

New claims 70, 71, and 72 have been added, and are directed to the pharmaceutical composition recited in former claim 47 (now cancelled).

New claim 73 has been added. Claim 73 defines an antibody by its 6 CDR regions (SEQ ID NOs: 33-38) from Krix-1 and by a deglycosylation at position 3 in the CDR1 region of the immunoglobulin variable heavy chain including the sequence of SEQ ID NO:33. Claim 73 recites an "antigen binding fragment." Support for this feature is found, for example, in the definition bridging pages 19 and 20 of the WO 2005/016455 publication. Here, the specification states:

> **"Antigen binding region"** as used herein refers to the region of an antibody involved in the binding of the antigen. More in particular, the antigen binding region can be determined as the amino acids and their substituents which contact through non-covalent bonding amino acids or molecules of the target protein.

And, at page 7, lines 27-30, states:

> The present invention further relates to inhibitory antibodies or fragments thereof obtained by the method of the invention, with modified glycosylation and a modified inhibitory activity, characterised in that the **affinity of said antibodies or fragments thereof** for their target protein is substantially unaffected. (Emphasis added.)

It is apparent that fragments of antibodies which have an affinity for their target protein are antigen binding fragments.

The unmodified antibody (Krix -1) is described in the specification as filed, for example, in the definition at page 20, lines 3-4, of the WO 2005/016455 publication. Here, the specification states:

> **Nomenclature:** the monoclonal antibody KRIX-1 produced in a lymphoblastoid cell line (LCL) is called Krix-1.

New claim 73 further refers to the glycosylation site by reference to the sequence of CDR1 of the immunoglobulin variable heavy chain. Support for this feature is found, for example, at page 12, lines 5-7, of the WO 2005/016455 publication. Here, the specification states:

> More particularly the pharmaceutical compound comprises one or more monoclonal antibodies which have been modified in the glycosylation in the region Asn47-Thr49.

The state of glycosylation at Asn47 is indicated in Figure 17 of the application as filed with an asterisk.

No new matter has been added by the present amendment.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Amendments to the specification

The title has been amended to reflect the presently claimed subject matter. No new

matter has been added by this amendment.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 34-40, 42-45, 47, and 58-64 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of enablement in the application as filed. The Office states (pages 4 and 5):

> [T]he specification, while being enabling for ... an antibody that binds FVIII and comprises the six CDRs of SEQ ID NOs:33-38 wherein the glycosylation site at positions 3 and/or 5 of SEQ ID NO:33 is mutated, ... an antibody that binds FVIII and comprises SEQ ID NO:2, and an antibody that binds FVIII and comprises SEQ ID NO:2 wherein SEQ ID NO:2 is mutated such that position 3 of CDR1 is mutated from N to Q, E, or D or position 5 is mutated from T to A, does not reasonably provide enablement for more.

Applicants address each basis for the enablement rejection as follows.

As an initial matter, Applicants note that claims 34 to 45, 47, and 61 to 63 have been cancelled. Rejection of these claims therefore is moot. The remaining claims have been amended as follows.

Claim 47 has been replaced by new claims 68, 69, and 70, which are now dependent from claim 58, 64, and 66, respectively.

Claim 58 has been re-written in independent form. Claim 58, as amended, is directed to an antibody which is defined by its variable heavy and light chain sequences, and contains a mutation of Asn47 and/or Thr49 of SEQ ID NO:2 or requires deglycosylation at Asn47 of SEQ ID NO:2.

Claim 64 has been re-written in independent form. Claim 64, as amended, is directed to an antibody, which is defined by the 6 CDR regions in the variable heavy and light chain, and mutations in the glycosylation site at position 3 and/or 5 in the CDR1 region of the variable heavy chain sequence of SEQ ID NO:33 or deglycosylation of Asn

at position 3 in the CDR1 region of the variable heavy chain sequence of SEQ ID NO:33.

Further claims 58 and 64, as amended, and new claims 66 and 73 recite the mutation of particular residues in the glycosylation consensus site or the deglycosylation at a particular Asn residue. The present claims recite mutations at positions 3 and/or 5 and no longer recite position 4. Applicants submit that claims 58, 64, and new claims 66 and 73 are directed to subject matter that the Office has indicated to be enabled by the application as filed. The enablement rejection may be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Applicants request that, upon an indication that the currently examined product claims are allowable, withdrawn process claims that require all of the limitations of the allowable product claims be considered for rejoinder.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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